CLAIMS

1. A method of identifying an agent that modulates the function of an apoptosis-associated polypeptide having a sequence as set out in Table 1B, the method comprising:

(a) providing a sample containing an apoptosis-associated polypeptide having a sequence as set out in Table 1B, and a candidate agent and incubating under conditions to permit binding of the candidate agent to the polypeptide;

(b) measuring the binding of the apoptosis-associated polypeptide having a sequence as set out in Table 1B to the candidate agent in the sample; and

(c) comparing the binding of the apoptosis-associated polypeptide having a sequence as set out in Table 1B to the candidate agent in the sample with the binding of the polypeptide having a sequence as set out in Table 1B to a control agent, wherein the control agent is known to not bind to the polypeptide having a sequence as set out in Table 1B;

wherein an increase in the binding of the apoptosis-associated polypeptide having a sequence as set out in Table 1B to the candidate agent in the sample relative to the binding of the apoptosis-associated polypeptide having a sequence as set out in Table 1B to the control agent indicates that the candidate agent modulates the function of the apoptosis-associated polypeptide having a sequence as set out in Table 1B.

2. A method of identifying an inhibitor of an apoptosis-associated protein that is encoded by a gene selected from Table 1B, comprising providing a preparation containing said encoded protein; incubating the preparation with a test agent to be

screened under conditions to permit binding of the test agent to the protein; determining whether the test agent interacts with the protein by detecting the presence or absence of a signal generated from the interaction of the agent with the protein, and thereby determining whether the test agent inhibits the apoptosis-associated protein.

3. The method according to claim 2 wherein the preparation containing the protein comprises a cell expressing the protein.

4. A method of identifying an inhibitor of an apoptosis-associated protein kinase that is encoded by a protein kinase gene selected from Table 1B, comprising providing a preparation containing said encoded protein kinase; incubating the preparation with a test agent to be screened under conditions to permit binding of the test agent to the protein kinase; determining whether the test agent interacts with the protein kinase by detecting a change in the phosphotransferase activity of the protein kinase, and thereby determining whether the test agent inhibits the apoptosis-associated protein kinase.

5. A method of identifying an inhibitor of an apoptosis-associated cell surface receptor protein that is encoded by a gene selected from Table 1B, comprising providing a cell expressing on its surface a protein that is encoded by cell surface receptor gene selected from Table 1B, said protein being associated with a second component capable of providing a detectable signal in response to the binding of an agent to said protein; contacting with an test agent to be screened under conditions to permit binding to the protein; and determining whether the agent binds to and inhibits the protein, by detecting the presence or absence of a signal generated from the interaction of the compound with the protein and thereby determining whether the test agent inhibits the activity of the apoptosis-associated cell surface receptor protein that is encoded by a gene selected from Table 1B.

6. The method according to claim 5 wherein the second component capable of providing a detectable signal is a G-protein.

7. The method according to claim 6 wherein the G-protein is a Gi, Go, Gs, G_{16}, G_{15}, Gq or G_{12-13} G-protein.

8. A process for determining whether a chemical compound specifically binds to and inhibits an apoptosis-associated protein that is encoded by a gene selected from Table 1B, which comprises contacting cells producing a second messenger response and expressing the protein that is encoded by a gene selected from Table 1B, wherein such cells do not normally express said protein, with the chemical compound under conditions suitable for inhibition of the protein, and measuring the second messenger response in the presence and in the absence of the chemical compound, a change in the second messenger response in the presence of the chemical compound indicating that the compound inhibits the apoptosis-associated protein that is encoded by a gene selected from Table 1B.

9. The process according to claim 8, wherein the second messenger response comprises chloride channel activation, a change in intracellular calcium ion levels, a release of inositol phosphate, a release of arachidonic acid, GTPγS binding, activation of MAP kinase, cAMP accumulation, a change in intracellular potassium ion levels, or a change in intracellular sodium ion levels.

10. The process according to claim 8 wherein the second messenger response is measured by a change in reporter gene activity.

11. The process according to claim 10 wherein the reporter gene is selected from secreted alkaline phosphatase, luciferase, and β-galactosidase.

12. A method of identifying an activator of apoptosis, comprising providing a preparation containing a protein that is encoded by a gene selected from Table 1B; incubating the preparation with a test agent to be screened under conditions to permit binding of the test agent to the protein; determining whether the test agent binds to, and inhibits the protein, by detecting the presence or absence of a signal generated from the interaction of the agent with the protein, and determining whether any test agent that inhibits the protein is an activator of apoptosis.

13. A method of identifying an inhibitor of tumor cell proliferation, comprising providing a preparation containing a protein that is encoded by a gene selected from Table 1B; incubating the preparation with a test agent to be screened under conditions to permit binding of the test agent to the protein; determining whether the test agent binds to, and inhibits the protein, by detecting the presence or absence of a signal generated from the interaction of the agent with the protein, and determining whether any test agent that inhibits the protein is an inhibitor of tumor cell proliferation.

14. A method for identifying an agent that inhibits tumor cell growth, which comprises determining whether a test agent interacts with a protein that is encoded by a gene selected from Table 1B in a preparation comprising the encoded protein, and determining whether any agent that interacts with the encoded protein is an inhibitor of tumor cell growth.

15. A method for identifying an agent that inhibits tumor growth, which comprises determining whether a test agent interacts with a protein that is encoded by a gene selected from Table 1B in a preparation comprising the encoded protein, and determining whether any agent that interacts with the encoded protein is an inhibitor of tumor growth.

16. A method for identifying an agent that has pro-apoptotic activity, which comprises determining whether a test agent modulates the activity or expression of a protein that is encoded by a gene selected from Table 1B, and determining whether any agent that modulates said activity or expression is an activator of apoptosis.

17. A method for identifying an agent that inhibits tumor cell proliferation, which comprises determining whether a test agent modulates the activity or expression of a protein that is encoded by a gene selected from Table 1B, and determining whether any agent that modulates said activity or expression is an inhibitor of tumor proliferation.

18. A method for identifying an agent that inhibits tumor cell growth, which comprises determining whether a test agent modulates the activity or expression of a protein that is encoded by a gene selected from Table 1B, and determining whether any agent that modulates said activity or expression is an inhibitor of tumor cell growth.

19. A method for identifying an agent that inhibits tumor growth, which comprises determining whether a test agent modulates the activity or expression of a protein that is encoded by a gene selected from Table 1B, and determining whether any agent that modulates said activity or expression is an inhibitor of tumor growth.

20. The method according to any of claims 16-19, wherein the test agent is selected from a low molecular weight organic molecule, an antibody or antibody fragment, an antisense oligonucleotide, a small inhibitory dsRNA, and a ribozyme.

21. An inhibitor of tumor cell proliferation, tumor cell growth or tumor growth, identified by a method according to any of claims 14, 15, 17, 18 or 19.

22. An inhibitor of tumor cell proliferation or tumor growth as in claim 21, wherein the inhibitor is selected from a low molecular weight organic molecule, an antibody or

antibody fragment, an antisense oligonucleotide, a small inhibitory dsRNA, and a ribozyme.

23. A method of inhibiting tumor growth in a mammal in recognized need of such treatment, said method comprising administering to said mammal in recognized need of such treatment, an inhibitor of the activity or expression of an apoptosis-associated protein that is encoded by a gene selected from Table 1B, wherein said administering is in an effective amount to reduce tumor growth in said mammal.

24. The method of claim 23, wherein the inhibitor is selected from a low molecular weight organic molecule, an antibody or antibody fragment, an antisense oligonucleotide, a small inhibitory dsRNA and a ribozyme.

25. A method of stimulating apoptosis of tumor cells in a mammal in recognized need of such treatment, said method comprising administering to said mammal in recognized need of such treatment, an inhibitor of the activity or expression of a protein that is encoded by a gene selected from Table 1B, wherein said administering is in an effective amount to stimulate apoptosis of tumor cells in said mammal.

26. The method of claim 25, wherein the inhibitor is selected from a low molecular weight organic molecule, an antibody or antibody fragment, an antisense oligonucleotide, a small inhibitory dsRNA and a ribozyme.

27. A method of inhibiting tumor cell proliferation in a mammal in recognized need of such treatment, said method comprising administering to said mammal in recognized need of such treatment, an inhibitor of the activity or expression of a protein that is encoded by a gene selected from Table 1B, wherein said administering is in an effective amount to reduce tumor cell proliferation in said mammal.

28. The method of claim 27, wherein the inhibitor is selected from a low molecular weight organic molecule, an antibody or antibody fragment, an antisense oligonucleotide, a small inhibitory dsRNA and a ribozyme.

29. A method of preparing a composition comprising a chemical compound which specifically binds to and inhibits an apoptosis-associated protein that is encoded by a gene selected from Table 1B, which comprises contacting cells expressing the apoptosis-associated protein that is encoded by a gene selected from Table 1B, wherein such cells do not normally express the encoded protein, with a test chemical compound under conditions suitable for binding of such a compound to the protein, detecting specific binding to and inhibition of the encoded protein by the test chemical compound, and admixing the test chemical so identified, or a functional analog or homolog of said test chemical, with a carrier, thereby preparing said composition.

30. A method of preparing a composition comprising a chemical compound which specifically inhibits an apoptosis-associated protein that is encoded by a gene selected from Table 1B, which comprises contacting an apoptosis-associated protein that is encoded by a gene selected from Table 1B with a test chemical compound under conditions suitable for binding of such a compound to the protein, detecting specific inhibition of the protein by the test chemical compound, and admixing the test chemical so identified, or a functional analog or homolog of said test chemical, with a carrier, thereby preparing said composition.

31. A method for identifying neoplasias responsive to treatment with compounds that selectively inhibit neoplasia, comprising exposing a sample of the neoplasia to a compound that has inhibitory activity on an apoptosis-associated protein that is encoded by a gene selected from Table 1B, and determining whether the compound inhibits the neoplasia.

32. A method for identifying neoplasias responsive to treatment with compounds that selectively inhibit neoplasia, comprising (a) removing a sample of neoplastic tissue from a patient, (b) growing cells from the sample as explants in vitro, (c) contacting a sample of said cells with a compound that has inhibitory activity on an apoptosis-associated protein that is encoded by a gene selected from Table 1B, (d) comparing the growth of the cells in the presence of the compound with the growth of cells in the absence of the compound, and (e) determining whether the growth of the neoplasia is sensitive to inhibition by the compound.

33. A method for identifying neoplasias responsive to treatment with an inhibitor of an apoptosis-associated protein that is encoded by a gene selected from Table 1B, comprising determining the level of the protein that is encoded by a gene selected from Table 1B in a sample of neoplastic tissue, wherein an elevated level of the apoptosis-associated protein that is encoded by a gene selected from Table 1B in the neoplastic tissue, relative to normal tissue, is indicative that the neoplasia has potential for being treated by an inhibitor of the apoptosis-associated protein that is encoded by a gene selected from Table 1B.

34. The method of claim 33 wherein the determination of the level of the protein that is encoded by a gene selected from Table 1B in the neoplastic tissue comprises determining the amount of the protein for the protein that is encoded by a gene selected from Table 1B in the neoplastic tissue sample.

35. The method of claim 33 wherein the determination of the level of the protein that is encoded by a gene selected from Table 1B in the neoplastic tissue comprises determining the amount of mRNA encoding for the protein that is encoded by a gene selected from Table 1B in the neoplastic tissue sample.

36. The method of claim 33 wherein the determination of the level of the protein that is encoded by a gene selected from Table 1B in the neoplastic tissue comprises

determining the biochemical activity of the protein that is encoded by a gene selected from Table 1B in the neoplastic tissue sample.

37. A method for identifying neoplasias from a patient responsive to treatment with an inhibitor of an apoptosis-associated protein that is encoded by a gene selected from Table 1B comprising the steps of:
a) obtaining a suspected neoplasic tissue sample from the patient;
b) contacting the sample with an antibody that is immunoreactive with the apoptosis-associated protein that is encoded by a gene selected from Table 1B under conditions effective to allow the formation of immune complexes; and
c) detecting the complexes thus formed, wherein an elevated amount of the apoptosis-associated protein that is encoded by a gene selected from Table 1B in the neoplastic tissue, relative to normal tissue, is indicative that the neoplasia has potential for being treated by an inhibitor of the apoptosis-associated protein that is encoded by a gene selected from Table 1B.

38. A method for identifying neoplasias responsive to treatment with compounds that selectively inhibit neoplasia, comprising (a) removing a sample of neoplastic tissue from a patient, (b) growing cells from the sample as explants in vitro, (c) contacting a sample of said cells with a compound that has inhibitory activity against an apoptosis-associated protein that is encoded by a gene selected from Table 1B, (d) comparing the number of apoptotic cells in the presence of the compound with the number of apoptotic cells in the absence of the compound, and (e) determining whether the compound promotes an increase in apoptosis in the neoplasia.

39. A method of detecting the presence in a sample of an apoptosis-associated polypeptide having a sequence as set out in Table 1B, the method comprising:

(a) bringing the biological sample containing DNA or RNA into contact with a probe comprising a fragment of at least 15 nucleotides of a nucleic acid having a sequence as set out in Table 1B under hybridizing conditions; and

(b) detecting a duplex formed between the probe and nucleic acid in the sample;

wherein detection of a duplex indicates the presence in the sample of an apoptosis-associated polypeptide having a sequence as set out in Table 1B.

40. A method of detecting the presence in a sample of an apoptosis-associated polypeptide having a sequence as set out in Table 1B, the method comprising:

(a) providing an antibody capable of binding to the apoptosis-associated polypeptide having a sequence as set out in Table 1B;

(b) incubating a biological sample with said antibody under conditions which allow for the formation of an antibody-antigen complex; and

(c) detecting an antibody-antigen complex comprising said antibody;

wherein detection of an antibody-antigen complex indicates the presence in the sample of an apoptosis-associated polypeptide having a sequence as set out in Table 1B.

41. A method of modulating apoptosis in a cell, the method comprising:

(a) transforming into the cell a double-stranded nucleic acid having a sequence as set out in Table 1B or a complement thereof, wherein the nucleic acid sequence is operably linked to a regulatory sequence; and

(b) culturing the cell under conditions whereby the nucleic acid sequence is expressed;

thereby modulating apoptosis in the cell.

42. A method of modulating apoptosis in a cell, the method comprising:

(a) transforming into the cell a double-stranded nucleic acid sequence encoding a polypeptide having a sequence as set out in Table 1B, wherein the nucleic acid sequence is operably linked to a regulatory sequence; and

(b) culturing the cell under conditions whereby the nucleic acid sequence is expressed;

thereby modulating apoptosis in the cell.

43. A method of modulating apoptosis in a cell, the method comprising:

(a) transforming into the cell a double-stranded nucleic acid sequence encoding a polypeptide having at least 80% sequence identity with a polypeptide having a sequence as set out in Table 1B, wherein the nucleic acid sequence is operably linked to a regulatory sequence; and

(b) culturing the cell under conditions whereby the nucleic acid sequence is expressed;

thereby modulating apoptosis in the cell.

44. A method of modulating apoptosis in a cell, the method comprising:

(a) transforming into the cell an isolated nucleic acid molecule comprising a regulatory sequence operably linked to a nucleic acid sequence that encodes a ribonucleic acid (RNA) precursor, wherein the precursor comprises:

(i) a first stem portion comprising a 15 to 40 nucleotide long sequence that is identical to 15 to 40 consecutive nucleotides of a sequence as set out in Table 1B;

(ii) a second stem portion comprising a 15 to 40 nucleotide long sequence that is complementary to 15 to 40 consecutive nucleotides of a sequence as set out in Table 1B, and wherein the first and second stem portions can hybridize with each other to form a duplex stem; and

(iii) a loop portion that connects the two stem portions;

(b) culturing the cell under conditions whereby the nucleic acid sequence is expressed;

thereby modulating apoptosis in the cell.

45. The method of claims 41-44, where the nucleic acid sequence is a nucleic acid having a sequence as set out in Table 1B, or a complement thereof.

46. The method of claims 41-44, wherein the nucleic acid sequence encodes a polypeptide having a sequence as set out in Table 1B.

47. The method of claims 41-44, wherein the nucleic acid encodes a polypeptide having at least 80% sequence identity to a polypeptide having a sequence as set out in Table 1B.

48. The method of claims 41-44, wherein apoptosis is decreased.

49. The method of claims 41-44, wherein apoptosis is increased.

50. An isolated RNA precursor encoded by a nucleic acid sequence having a sequence as set out in Table 1B.

51. A composition comprising, as a biologically active ingredient, the RNA precurser of claim 50.

52. A host cell transformed with one of the following: a) a double-stranded nucleic acid having a sequence as set out in Table 1B or a complement thereof, wherein the nucleic acid sequence is operably linked to a regulatory sequence; b) a double-stranded nucleic acid sequence encoding a polypeptide having a sequence as set out in Table 1B, wherein the nucleic acid sequence is operably linked to a regulatory sequence; c) a double-stranded nucleic acid sequence encoding a polypeptide having at least 80% sequence identity with a polypeptide having a sequence as set out in Table 1B, wherein the nucleic acid sequence is operably linked to a regulatory sequence; or d) an isolated nucleic acid molecule comprising a regulatory sequence operably linked to a nucleic acid sequence that encodes a ribonucleic acid (RNA) precursor, wherein the precursor comprises: (i) a first stem portion comprising a 15 to 40 nucleotide long sequence that is identical to 15 to 40 consecutive nucleotides of a sequence as set out in Table 1B; (ii) a second stem portion comprising a 15 to 40 nucleotide long sequence that is complementary to 15 to 40 consecutive nucleotides of a sequence as set out in Table 1B, and wherein the first and second stem portions can hybridize with each

other to form a duplex stem; and (iii) a loop portion that connects the two stem portions.

53. A method for providing a mammal with an anti-proliferative protein, the method comprising introducing into the mammal a mammalian cell transformed with one of a) a double-stranded nucleic acid having a sequence as set out in Table 1B or a complement thereof, wherein the nucleic acid sequence is operably linked to a regulatory sequence; b) a double-stranded nucleic acid sequence encoding a polypeptide having a sequence as set out in Table 1B, wherein the nucleic acid sequence is operably linked to a regulatory sequence; c) a double-stranded nucleic acid sequence encoding a polypeptide having at least 80% sequence identity with a polypeptide having a sequence as set out in Table 1B, wherein the nucleic acid sequence is operably linked to a regulatory sequence; or d) an isolated nucleic acid molecule comprising a regulatory sequence operably linked to a nucleic acid sequence that encodes a ribonucleic acid (RNA) precursor, wherein the precursor comprises: (i) a first stem portion comprising a 15 to 40 nucleotide long sequence that is identical to 15 to 40 consecutive nucleotides of a sequence as set out in Table 1B; (ii) a second stem portion comprising a 15 to 40 nucleotide long sequence that is complementary to 15 to 40 consecutive nucleotides of a sequence as set out in Table 1B, and wherein the first and second stem portions can hybridize with each other to form a duplex stem; and (iii) a loop portion that connects the two stem portions.

54. A method for treating a disease or condition characterized by abnormal apoptosis in mammalian tissue, the method comprising contacting the tissue with the RNA precursor of claim 50.

55. The method of claim 54, where the disease is cancer.

56. A pharmaceutical composition comprising, as an active ingredient, an apoptosis-associated nucleic acid having a sequence as set out in Table 1B, and a pharmaceutically-acceptable carrier.

57. A pharmaceutical composition comprising, as an active ingredient, an apoptosis-associated polypeptide having a sequence as set out in Table 1B, and a pharmaceutically-acceptable carrier.

58. A pharmaceutical composition comprising, as an active ingredient, an antibody to an apoptosis-associated nucleic acid having a sequence as set out in Table 1B, and a pharmaceutically-acceptable carrier.

59. A pharmaceutical composition comprising, as an active ingredient, an antibody to an apoptosis-associated polypeptide having a sequence as set out in Table 1B, and a pharmaceutically-acceptable carrier.

60. A method for diagnosing a disease or condition characterized by abnormal apoptosis in mammalian tissue, the method comprising contacting the tissue with the antibody of claims 58 or 59, and detecting an antibody/antigen complex, wherein said detection is indicative of said disease or condition.

61. A method for treating a disease or condition characterized by abnormal apoptosis in mammalian tissue, the method comprising contacting the tissue with an antagonist of an apoptosis-associated polypeptide having a sequence as set out in Table 1B.

62. A method for treating a disease or condition characterized by abnormal apoptosis in mammalian tissue, the method comprising contacting the tissue with an agonist of an apoptosis-associated polypeptide having a sequence as set out in Table 1B.

63. A kit for treating a disease or condition characterized by abnormal apoptosis in mammalian tissue, the kit comprising:

(a) a polypeptide encoded by a nucleic acid having a sequence as set out in Table 1B;

(b) a nucleic acid having a nucleotide sequence as set out in Table 1B; or

(c) an antibody recognising an epitope of a polypeptide of (a).

64. An array comprising at least two apoptosis genes having nucleic acid sequences having a sequence as set out in Table 1B.

65. The array of claim 64, wherein the nucleic acid sequences are DNA sequences.

66. The array of claim 64, wherein the nucleic acid sequences are RNA sequences.

67. An array comprising at least two apoptosis proteins having polypeptide sequences having a sequence as set out in Table 1B.